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| NGUYEN, Q | |
| ART UNIT | PAPER NUMBER |
| 1632 | 11 |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

PTO-90C (Rev.11/00)

1- File Copy

| Office Action Summary | Application No. 09/421,778 | Applicant(s) FULLER, JAMES T. |
|---|---|---|
| | Examiner Quang Nguyen | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on th cover sh t with the correspondenc addr ss --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *9,10,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17 and 20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicants' amendments filed on April 12, 2001 and April 27, 2001 in Paper Nos. 12 and 14 have been entered.

Claims 1-27 are pending in the present application. Applicants confirmed the election of Group I (Claims 1-8, 11-17 and 20-27) without traverse, whose nature of the invention is further clarified by Applicant in the Amendment filed in Paper No. Claims 9-10 and 18-19 are withdrawn from further consideration because they are directed to non-elected inventions.

Claims 1-8, 11-17 and 20-27 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

***Response to Amendments***

The rejection of claims 1-4, 7, 8, 11-17, 20-23 and 25-27 under 35 USC 102(b) as being anticipated by Lai et al. (DNA Cell Biol. 14:643-651) is withdrawn.

The rejection of claims 1, 5, 7, 8 and 12 under 35 USC 102(b) as being anticipated by Laube et al. (Human Gene Ther. 5:853-862, 1994) is withdrawn.

### *Claim Rejections - 35 USC § 102*

Claims 1, 12-14 and 25-27 are rejected under 35 U.S.C. 102(a) as being anticipated by A-Mohammadi & Hawkins (Gene therapy 5:76-84, 1998) for the same reasons set forth in the previous Office Action in Paper No. 6 (pages 13).

The claims are drawn to a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence, a vector comprising the same nucleic acid construct, and a method of obtaining expression in mammalian cells of a polypeptide of interest using the same. Claims 13 and 14 are drawn to the same method wherein the minimal promoter sequence consists essentially of a hCMV immediate early promoter sequence, a pseudorabies virus early promoter sequence, a simian cytomegalovirus immediate early promoter sequence or a functional variant thereof, and wherein the minimal promoter sequence consists essentially of the sequence spanning positions 0 to –118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence, respectively. It is noted that the scope of claim 1 and its dependent claims encompasses both *in vitro* and *in vivo* methods of obtaining expression in mammalian cells of an antigen of interest.

With respect to an *in vitro* method, A-Mohammadi & Hawkins disclosed the construction and analysis of tetracycline-regulatable plasmid vectors comprising a bidirectional minimal promoter of $pCMV^{*-1}$ operably linked to coding sequences (See Fig. 1). An enhancerless positive feedback regulatory vector construct pSialV transcribing both the tetracycline-controlled transactivator (tTA) and mGM-CSF from a modified tTA-responsive bidirectional promoter demonstrated over 200 fold gene regulation in HeLa cells (See Fig. 5). The maximal transcriptional activity of pSialV was comparable to that of intact CMV IE promoter and its basal activity was repressed to the leakiness of the tetracycline-responsive promoter in response to tetracycline. Since a functional variant encompasses truncated functional versions of the minimal promoter

sequence and functional fragments of a native promoter sequence (see instant specification on page 10, lines 27-29 and page 11, lines 1-2), the teachings of A-Mohammadi & Hawkins meet the required elements in the claims. With respect to the limitation recited in claims 14 and 22, "consisting essentially of the sequence spanning positions 0 to –118 of the hCMV.....or a functional variant of the said spanning sequence", the claim reads over a bidirectional minimal promoter of $pCMV^{*-1}$ described by A-Mohammadi & Hawkins for which the instant specification has no written support for. Therefore, the reference anticipates the claimed invention.

Claims 1, 12-14 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996) for the same reasons set forth in the previous Office Action in Paper No. 6 (pages 13-14).

With respect to an *in vitro* method, Hofmann et al. disclosed a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence $(TetO)_7$ fused to the human CMV immediate early minimal promoter $P_{hCMV^{*-1}}$ (See Fig. 1). Analysis of transduced C57BL/6 primary myoblasts revealed that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude. In this instant, beta-galactosidase is the polypeptide of interest. The human CMV immediate early minimal promoter $P_{hCMV^{*-1}}$ falls within the scope of a functional variant, the disclosure of Hofmann et al fulfilled the required elements in the claims. With respect to the limitation recited in claims 14 and 22, "consisting essentially of the sequence spanning positions 0

to 118 of the hCMV.....or a functional variant of the said spanning sequence", the claim reads over the $P_{hCMV^{*}-1}$ promoter disclosed by Hofmann et al. for which the instant specification has no written support for. Thus, the reference anticipates the instant claimed invention.

***Response to Arguments***

Applicants' arguments related to the above rejection in the Amendment filed on April 12, 2001 in Paper No. 12 (pages 13-14) have been fully considered.

Applicants mainly argued that that the cited references do not teach a minimal promoter linked to an antigen-encoding sequence. Examiner respectfully finds Applicants' argument to be unpersuasive because the sequences encoding transactivator (tTA) and mGM-CSF taught by A-Mohammadi & Hawkins or the lacZ sequence disclosed by Hofmann et al. are sequences encoding for antigens because upon administering beta-galactosidase or the transactivator into an individual that normally does not naturally habor such gene products, a host immunological response will be elicited. As defined by the instant specification, an antigen refers to any agent, generally a macromolecule, which can elicit an immunological response in an individual (page 7, lines 7-8). Moreover, these sequences are operably linked to the minimal promoter of $pCMV^{*-1}$.

With respect to the A-Mohammadi & Hawkins reference, Applicant would like to verify the actual publication date. The article appeared in the January issue of Gene Therapy which is prior to the effective filing date of the present application, 10/19/1998.

Accordingly, claims 1, 12-14 and 25-27 are rejected for the reasons stated above.

Upon further consideration of this application, following is a new ground of rejection.

***Claim Rejections - 35 USC § 112***

Claims 1-4, 6-8, 11-17 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a native minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said mammalian cells and the same method *in vivo* for non-humans, wherein said nucleic acid construct is delivered by intramuscular, intravenous, intradermal injections or transdermal particle delivery; and coated particles suitable for use in particle-mediated nucleic acid immunisation, which particles comprise carrier particles coated with the same nucleic acid construct; a particle acceleration device being loaded with the same coated particles, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said mammalian cells, coated particles comprising carrier particles coated with the same nucleic acid construct, a particle accelerating device loaded with the same coated particles and the same nucleic acid construct .

The specification discloses by exemplification the construction of Hepatitis B surface antigen (HbsAg) expression cassettes driven by full-length or minimal promoter systems (with or without enhancer, respectively) derived from simian CMV, human CMV and pseudorabies virus (PRV). The DNA constructs were coated onto gold carrier particles and administered to Balb/c mice using a particle-mediated delivery technique. Analysis of anti-HbsAg antibodies in sera taken from vaccinated mice six weeks later, revealed that minimal promoter system gave a significant improvement in antibody titer over the fully enhanced promoter system.

The above evidence has been noted and considered. However, the evidence can not reasonably extrapolated to the instant broadly claimed invention for the following reasons. The instant claims encompass both *in vitro* and *in vivo* methods for obtaining expression in mammalian cells of an antigen of interest using the nucleic acid construct having the minimal promoter sequence of the present invention. With regard to the *in vivo* method, when read in light of the specification the sole purpose for such a method is to induce a protective immune response in a host against viral, bacterial,

parasite or fungal pathogen. Besides this contemplated use, it is unclear from the instant specification what is the purpose of merely expressing an antigen of interest *in vivo*. Enablement requires the specification to teach how to make and use the claimed invention. Therefore, an embodiment of the instant claims falls within the art of genetic immunization which at about the effective filing date of the present application was considered to be an emerging technology (Chattergoon et al., FASEB J. 11:753-763, 1997, Cited previously). The instant claims encompass any and all routes of delivering the nucleic acid construct having the minimal promoter. However, apart from disclosing that an enhanced anti-HbsAg antibody titers was obtained in a mouse model via the particle-mediated delivery technique, the specification fails to provide sufficient guidance demonstrating that a similar enhanced immunological response could be achieved for any other routes of delivery, let alone the therapeutic effects that Applicant contemplates to achieve *in vivo*. For example, as the claims being written, it is highly unlikely that the naked nucleic acid construct could be effectively transferred into mammalian cells via inhalation, oral or mucosal routes of delivery to express the encoded antigen of interest at an effective amount to elicit the desired host immune responses. This is because said nucleic acid construct could be subjected to degradation prior to being transferred to the appropriate cells for expression and induction of the desired immune responses. Since the instant specification fails to provide specific parameters or conditions utilized to achieve the desired effects by such means of delivery, and the prior arts at the effective filing date of the present application also do not provide such guidance, it would have required undue experimentation for

one skilled in the art to make and use the instant broadly claimed invention. Furthermore, McCluskie et al. (Mol. Med. 5:287-300, 1999, Cited previously) noted that the route of administration of plasmid DNA vaccines influences the strength and nature of immune responses in mice and non-human primates, and that optimal dose and immunization schedule most likely vary between species (See Conclusions of the abstract). More recently, Leitner et al. (Vaccine 18:765-777, 2000) stated that "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Thus, it appears that attainment of therapeutic effects *in vivo* via genetic immunization continues to be unpredictable.

The breadth of the instant claims encompasses a functional variant of a minimal promoter sequence consisting essentially of a human CMV immediate early promoter sequence, a pseudorabies (PRV) early promoter region and a simian cytomegalovirus (sCMV) immediate early promoter sequence. There is a high degree of unpredictability associated with the make and use of this claimed embodiment. In discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). This unpredictability is further underscored by the fact that the relationship between the sequence of a peptide and its tertiary structure is not well understood and is not predictable (Ngo et al., *In* K. Merz et al., ed. "The protein folding

problem and tertiary structure prediction", Birkhauser, 1994, 491-495). Similar unpredictability also occurs in the relationship between the nucleotide sequence of a minimal promoter and its promoting activity for the present invention. Apart from the disclosure using native minimal promoters derived from simian CMV, human CMV and pseudorabies virus (PRV), the instant specification does not teach which "particular" nucleotide residue at which position in the minimal promoter sequences to be substituted, deleted, inserted and in which combinations such that the resulting variants still possess functional promoting activity. With the lack of guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the full breadth of the instant claimed invention.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues raised above, the unpredictability of the genetic immunization with regard to achieving therapeutic effects, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

***Response to Arguments***

Applicant' s arguments related to the above rejection in the Amendment filed on April 12, 2001 in Paper No. 12 (pages 5-11) have been fully considered.

Applicant basically argued that the claims are drawn to a method for obtaining expression of an antigen sequence, and that Applicant has not recited a method for absolutely preventing all infection and disease. Therefore, the instant specification is

fully enabled. With respect to a new ground of rejection above, Examiner respectfully finds Applicant's argument to be unpersuasive for the following reasons. Examiner agrees with Applicant that the claimed method is not directed to one for absolutely preventing all infection and disease, and that the claims are drawn to a method for obtaining expression of antigen sequence. However, with respect to the *in vivo* scope of the method claims, when read in light of the specification the sole purpose for such an *in vivo* method is to induce a protective immune response in a host against viral, bacterial, parasite or fungal pathogen or at least some type of therapeutic effects. Besides this contemplated use, it is unclear from the instant specification what is the purpose of merely expressing an antigen of interest *in vivo*. As such, with claim 6 specifically directed to the method in a human, the instant specification is not enabled because the attainment for therapeutic effects *in vivo* via genetic immunization in human continues to be unpredictable in the year 2000, let alone at the effective filing date of the present application as evidenced by Leitner et al. who stated that "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Moreover, as noted in the previous Office Action, McCluskie et al. stated that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, non of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." (col. 2, last

paragraph, page 296). Since the instant specification fails to provide sufficient guidance for a skilled artisan on achieving any therapeutic effects in human using the nucleic acid construct comprising the minimal promoter of this invention for immunization, it would therefore require undue experimentation to make and use the claimed invention.

Accordingly, claims 1-4, 6-8, 11-17 and 20-23 are rejected under 35 U.S.C. 112, first paragraph for the reasons stated above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1, 5, 6, 13-14, 15, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 5 and 6, the phrase "the cells are reintroduced into the subject" is unclear and it renders the claims indefinite. There is no nexus between this step and the expression in mammalian cells of an antigen of interest recited in the preamble of claim 1 from which both claims 5 and 6 are dependent upon. As far as the preamble of claim 1 is concerned, the methods in claims 5 and 6 are completed when the construct is delivered *ex vivo* into cells taken from a subject. Clarification is requested. Should Applicant intend to claim an *ex vivo* method, Examiner suggests an independent claim reciting such a method.

In claims 13, 14, 21 and 22, it is unclear what is encompassed by the term "a functional variant ". Although the term is vaguely defined in the instant specification on

page 10, line 27 continues to line 2 on page 11, it is still not clearly defined because it may vary from a native promoter sequence, and may encompass functional fragments of a native promoter sequence. What else does it encompass? Therefore, the metes and bounds of the claims can not be clearly determined. Clarification is requested.

Claims 14 and 22 recite the limitation "the hCMV immediate early promoter region" in lines 2 and 3 of the claims. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of the hCMV immediate early promoter region in claims 13 and 21 from which claims 14 and 22 are dependent upon, respectively.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1).

The claims are directed to a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said

mammalian cells, coated particles comprising carrier particles coated with the same nucleic acid construct, a particle accelerating device loaded with the same coated particles and the same nucleic acid construct .

With respect to the enabled scope of the instant invention, Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of the regulatory element and under the transcriptional control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which may optionally be incorportated into the polynucleic acid sequence include enhancers, termination sequences and others (col. 5, lines 42-45 and lines 65-67). According to Molecular Biotechnology text book (Glick, B.R. & Pasternak, J.J., eds., 1994), a "promoter" is defined as a segment of DNA to which RNA polymerase attaches. It usually lies upstream of (5' to) a gene. A promoter sequence aligns the RNA polymerase so that

transcription will initiate at a specific site (page 475). While "enhancer" is defined as a DNA sequence that increases the transcription of a eukaryotic gene when they are both on the same DNA molecule. Also called enhancer element, enhancer sequence (page 461). As such, the DNA sequence utilized in the disclosed method of Johnston et al. can be one having a promoter without any enhancer, which meets the limitation of the "minimal promoter" of the instant invention which merely requires a promoter sequence without its endogenous enhancer. Exemplary promoters that Johnston et al. teach include the human alpha-actin promoter, the human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, the metallothionin gene promoter among others. Additionally, exemplary of genes which code for proteins or peptides which produce an immune response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14). Therefore, Johnston et al. anticipate the instant claimed invention.

Claims 24-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Gu et al. (U.S. Patent No. 6,200,751).

The claims are drawn to a purified, isolated minimal promoter sequence, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen of interest, a vector comprising the same nucleic acid construct, preferably a plasmid.

Gu et al. disclosed the isolation and uses of the minimal promoter of the endothelial cell protein C binding protein, EPCR, operably linked to a gene coding for a

protein of interest in expression vectors, including plasmid vectors, e.g. pEGFP1 (See col. 4, lines 24-36, lines 45-47; example 3, col. 5, lines 42-49 and the claims). According to Molecular Biotechnology text book (Glick, B.R. & Pasternak, J.J., eds., 1994), a "promoter" is defined as a segment of DNA to which RNA polymerase attaches. It usually lies upstream of (5' to) a gene. A promoter sequence aligns the RNA polymerase so that transcription will initiate at a specific site (page 475). While "enhancer" is defined as a DNA sequence that increases the transcription of a eukaryotic gene when they are both on the same DNA molecule. Also called enhancer element, enhancer sequence (page 461). As such, the promoter including a region resulting in selective expression in endothelial cells, between –1 and –220 based on the positions relative to the ATG encoding the first amino acid of the murine EPCR protein disclosed by Gu et al. (col. 1, lines 58-63, col. 4, lines 24-36) meets the limitation of the "minimal promoter" of the instant invention which merely requires a promoter sequence without its endogenous enhancer. The encoded green flurorescent protein in the pEGFP1 is an antigen because it is capable of inducing a host immune response in an individual that normally does not naturally habor said gene product. As defined by the instant specification, an antigen refers to any agent, generally a macromolecule, which can elicit an immunological response in an individual (page 7, lines 7-8). Therefore, Gu et al. anticipate the instant claimed invention.

It is noted that the same teachings are disclosed in WO98/20041 (IDS, AT-1).

***Claim R jections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 13-15, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1) in view of A-Mohammadi & Hawkins (Gene therapy 5:76-84, 1998) or Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996).

The claims are drawn to a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said mammalian cells; coated particles suitable for use in particle-mediated nucleic acid

immunisation, which particles comprises carrier particles coated with a nucleic acid construct comprising a minimal promoter sequence operably linked to a sequence encoding an antigen, the same method and coated particles wherein the minimal promoter sequence has the limitations recited in claims 13-15 and 21-22.

With respect to the enabled scope of the instant invention, Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of the regulatory element and under the transcriptional control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which **may optionally** be incorporated into the polynucleic acid sequence include **enhancers**, termination sequences and others (col. 5, lines 42-45 and lines 65-67). According to Molecular Biotechnology text book (Glick, B.R. & Pasternak, J.J., eds., 1994), a "promoter" is defined as a segment of DNA to which RNA polymerase attaches. It usually lies

upstream of (5' to) a gene. A promoter sequence aligns the RNA polymerase so that transcription will initiate at a specific site (page 475). While "enhancer" is defined as a DNA sequence that increases the transcription of a eukaryotic gene when they are both on the same DNA molecule. Also called enhancer element, enhancer sequence (page 461). As such, the DNA sequence utilized in the disclosed method of Johnston et al. can be one having a promoter without any enhancer, which meets the limitation of the "minimal promoter" of the instant invention which merely requires a promoter sequence without its endogenous enhancer. Exemplary promoters that Johnston et al. teach include the human alpha-actin promoter, the human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, the metallothionin gene promoter among others. Additionally, exemplary of genes which code for proteins or peptides which produce an immune response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14). However, Johnston et al. do not specifically teach a minimal promoter having the limitations recited in the claims.

A-Mohammadi & Hawkins disclosed the construction and analysis of tetracycline-regulatable plasmid vectors comprising a bidirectional minimal promoter of $pCMV^{*-1}$ operably linked to coding sequences (See Fig. 1). An enhancerless positive feedback regulatory vector construct pSialV transcribing both the tetracycline-controlled transactivator (tTA) and mGM-CSF from a modified tTA-responsive bidirectional promoter demonstrated over 200 fold gene regulation in HeLa cells (See Fig. 5). The maximal transcriptional activity of pSialV was comparable to that of intact CMV IE

promoter and its basal activity was repressed to the leakiness of the tetracycline-responsive promoter in response to tetracycline.

Hofmann et al. disclosed a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence $(TetO)_7$ fused to the human CMV immediate early minimal promoter $P_{hCMV*-1}$ (See Fig. 1). Analysis of transduced C57BL/6 primary myoblasts revealed that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude.

The human CMV immediate early minimal promoters $pCMV^{*-1}$ and $P_{hCMV*-1}$ disclosed by A-Mohammadi & Hawkins and Hoffman et al., respectively, fall within the scope of a functional variant, and with respect to the limitation recited in claim 22, "consisting essentially of the sequence spanning positions 0 to 118 of the hCMV.....or a functional variant of the said spanning sequence", the claim reads over these promoters for which the instant specification has no written support for.

Accordingly, at the time of the instant invention, it would have been obvious to an ordinary skilled artisan to use the truncated minimal promoters disclosed by A-Mohammadi & Hawkins or Hoffman et al. as the regulatory sequence providing the transcriptional control of the gene in the polynucleic acid sequence coating the microprojectiles taught by Johnston et al. One of ordinary skilled artisan would have been motivated to carry out the above modification because as suggested by A-Mohammadi & Hawkins that the enhancerless positive feedback regulatory vector (pSialV) offers an efficient gene regulation which is suitable for most applications,

especially gene therapy (See abstract). Additionally, Hoffmann et al. suggested that their single autoregulatory cassette containing the CMV minimal promoter allows rapid delivery of inducible genes and has broad applications (See abstract). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laube et al. (Human Gene Ther. 5:853-862, 1994; Cited previously) in view of A-Mohammadi & Hawkins (Gene therapy 5:76-84, 1998) or Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996).

The claims are drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest, and wherein the method comprises *ex vivo* deliverance into cells taken from a subject a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the polypeptide, and the cells are reintroduced into the subject.

With respect to the enabled scope of the instant invention, Laube et al. disclosed *ex vivo* transduction of autologous non-human primate rhesus monkey fibroblasts derived from skin biopsies with a retroviral vector encoding HIV-1 IIIB ENV/REV proteins, followed by the readministration of retroviral vector-transduced fibroblasts into the animals to generate cytotoxic T lymphocyte and antibody responses (See abstract). However, Laube et al. do not teach specifically the use of a minimal promoter for expressing the antigen of interest.

The teachings of A-Mohammadi & Hawkins and Hofmann et al. have been described in details above.

Accordingly, at the time of the instant invention, it would have been obvious to an ordinary skilled artisan to modify the method disclosed by Laube et al. by using the enhancerless positive feedback regulatory vector or the cassette of the retroviral construct taught by A-Mohammadi & Hawkins and Hofmann et al., respectively, to express HIV-1 IIIB ENV/REV proteins in the primary autologous fibroblasts with a reasonable expectation of success. One of ordinary skilled artisan would have been motivated to carry out the above modification because as suggested by as suggested by A-Mohammadi & Hawkins that the enhancerless positive feedback regulatory vector (pSialV) offers an efficient gene regulation which is suitable for most applications, especially gene therapy (See abstract). Additionally, Hoffmann et al. suggested that their single autoregulatory cassette containing the CMV minimal promoter allows rapid delivery of inducible genes and has broad applications (See abstract).. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

## ***Conclusions***

**No claim is allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

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PRIMARY EXAMINER